REMARKS

Claims 72 to 88 and 98 to 116 are under consideration. By this paper, claims 72, 74, 76 to 79, 82 to 88, 98, 99, 113 and 114 have been cancelled herein without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit of priority of the subject application. New claims 117 to 121, which depend from claim 73, have been added. Accordingly, upon entry of this paper, claims 73, 75, 80, 81, 100 to 112, and 115 to 121 are under consideration.

Regarding the Claim Amendments

The amendments to the claims are supported throughout the originally filed specification or were made to address informalities. In particular, the amendment to claim 73 to recite an antibody or functional fragment thereof "comprising a light chain (V_L) variable region sequence and a heavy chain (V_H) variable region sequence" was made to clarify that the antibody or functional fragment includes a light chain (V_L) variable region sequence and a heavy chain (V_H) variable region sequence, and is also supported, for example, at page 29, lines 20-25. The amendment to claim 73 to recite "neoplastic" was made to provide additional antecedent basis for the recited neoplastic cells. The amendment to the claims to recite "thereof" was made to clarify that the functional fragment is a fragment of the recited antibody. The amendment to claims 80 and 81 to depend from claim 73 instead of claim 72 was made due claim 72 being cancelled. The amendments to claims 100 to 106 and 111 to recite "light chain (V_L) variable region sequence is and/or "heavy chain (V_H) variable region sequence is" was made to provide antecedent basis for these respective terms recited in amended claim 73. Thus, as the claim amendments are supported throughout the originally filed specification or were made to address informalities, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claims

New claims 117 to 121 are supported throughout the originally filed specification. In particular, claims 117 to 120 are supported, for example, by originally filed claims 1 to 22, and at page 19, lines 9-15. Claim 121 is supported, for example, at page 16, lines 10-11. Thus, as claims 117 to 121 are supported by the originally filed specification, no new matter has been added and entry thereof is respectfully requested.

Regarding the Information Disclosure Statements

Applicants note that IDS filed February 17, 2009, has been considered. With respect to the IDS' filed November 17, 2008 and February 11, 2009, Applicants have resubmitted these IDS' in the requested format. Consideration of the listed references is respectfully requested.

Regarding the Objections to the Specification

The specification remains objected to due to the alleged absence of x-axis and y-axis labels for Figure 10A and 10B.

Applicants respectfully point out that the previous remarks concerning the x- and y-axis were inadvertently transposed, and regret any confusion. In Figures 10A and 10B, in view of the description on page 27, lines 16-25, the y-axis of 10A and 10B refers to tumor weight and tumor volume, respectively, and the circles along the x-axis appear to each represent a particular mouse. In terms of the circles for both SAM-6 treated and control being open, Applicants recognize that they are the both represented as open circles on Figure 10. Even so, in view of the description of the study results represented in Figure 10, which are clearly summarized in the Figure 10 description, one can "discern the effects of SAM-6 from the control." In particular, the description states that "According to Figure 10a the average weight of tumors of SAM-6 treated mice is 96.2 gram, while average weight of tumors of mice treated with the control antibody is 150.5 gram. Figure 10b shows that analysis of the volume of tumors corresponds to with the analysis of tumor weight. The average volume of tumors of SAM-6 treated mice is 126.3 mm^3, while average volume of tumors of mice treated with control antibody is 158.2 mm^3." Thus, even if Figure 10 in itself does not distinguish SAM-6 from control, clearly in view of the description one of skill in the art would knows the effect of SAM-6 compared to control. Applicants further note that submission of a revised Figure 10 or additional description of the results may prompt a rejection for addition of new matter, and respectfully request the Examiner's consideration in this respect. Thus, in view of the foregoing, Applicants submit that there is no need to amend the drawing description or Figure 10 and respectfully request withdrawal of the objection.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

ENABLEMENT

The rejection of claims 72 to 79, 82 to 88 and 98 to 116 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. According to the Patent Office, allegedly it would require undue experimentation to make and use the claimed invention.

The proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. In this regard, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands* 858 F.2d 731, 737 (Fed. Cir. 1988).

Here, in view of the guidance in the specification and knowledge and skill in the art at the time of the invention, antibody variants having the requisite activity could be produced and identified using routine methods disclosed in the specification or known in the art at the time of the invention without undue experimentation. Consequently, one skilled in the art could make the claimed antibodies and functional fragments that specifically bind to the recited epitope of the antigen expressed by at least one of the recited cells, that inhibit cell proliferation or that induce apoptosis, without undue experimentation.

First, the level of knowledge and skill in the art regarding making antibodies and functional fragments thereof was high. For example, methods of producing antibodies and amino acid variants without undue experimentation are disclosed in the specification (page 31, line 20, to page 36, line 26) and were also known in the art at the time of the invention. Methods of producing antibody fragments (*e.g.*, Fv, Fab, Fab' and $F(ab')_2$) were known in the art and were routine at the time of the invention. Methods of identifying antibodies and fragments that bind antigen without undue experimentation were also known in the art and are taught by the specification. In particular, routine methods for detecting antibody binding to antigen or cell lines, as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 47, line 8 to page 49, line 10; page 55, line 26, to page 57, line 29; and page 66, line 10, to page 68, line 24). Thus, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention, one skilled in the art could readily make antibodies and functional fragments without undue experimentation.

Claims 72 to 79, 82 to 88 and 98 to 116 are analogous to *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation. Likewise, undue experimentation would not be required to make variant antibodies and fragments that bind the epitope to which SAM-6 antibody binds given that 1) producing antibody variants and fragments was routine; and 2) cell binding, antibody competition, proliferation and apoptosis assays are disclosed in the specification and were also routine assays in the art at the time of the invention.

In regard to the statements in this Office Action (e.g., pages 9, 12 and 13) where allegedly one skilled in the art would not be able to produce antibodies absent "1) a complete structure, ii) a partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of antibodies that a) bind the epitope to which SAM-6 antibody binds, b) inhibits cell proliferation of 23132/87....cells and c) induces apoptosis of at least one of BXPC-3 and 23132/87 cells...." or a "structure function correlation for the claimed antibodies that would enable the ordinary artisan to predict making and using the broad scope of antibodies with a reasonable degree of certainty absent further experimentation...." or that "ordinary artisans could not predict the operability in the invention of any species other than the one disclosed," all of these statements are paraphrased from court decisions concerning the written description requirement, and do not reflect the proper standard for enablement under 35 U.S.C. §112 (e.g., *Regents of the University of California v. Eli Lily*, 119 F.3d 1559 (Fed. Cir. 1997); *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004); and *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002)). Thus, clearly the enablement standard applied by the Patent Office to the claims is incorrect.

Furthermore, claims where no antibody has ever been produced are routinely granted by the Patent Office. Thus, if claims covering antibodies where no antibody has been made and therefore where no antibody structure is known have been granted, surely knowledge of antibody structure or predicting the effects of particular variations on antibody binding is not required to satisfy the enablement requirement under 35 U.S.C. §112. Consequently, it is clear that the standard for enablement applied by the Patent Office to the claims is incorrect. Accordingly, Applicants respectfully request that the Patent Office apply the correct standard for enablement under 35 U.S.C. §112.

Here, making variant antibodies and functional fragments and identifying those with activity (e.g., binding, inhibit cell proliferation, etc.) are disclosed in the specification and/or was routine at the time of the invention. Thus, in view of the guidance in the specification and knowledge and skill in the art at the time of the invention, there is no need to "predict which variation would not compromise antigen binding specificity" in order to make variant antibodies and functional fragments. For example, the skilled artisan could simply introduce mutations in a heavy and/or light chain variable region (SEQ ID NOs:1 or 3) and then verify which antibodies and fragments bind to the epitope to which SAM-6 antibody binds (e.g., via competition binding). Consequently, one of skill in the art need not predict in advance the effect of any particular variation on binding in order to make variant antibodies and functional fragments.

As an example of how routine the methods of producing variant antibodies and identifying those having binding activity were at the time of the invention, previously submitted Exhibit A (Boder *et al.* (Proc. Nat'l Acad. Sci. USA 97:10701 (2000)) describe directed evolution of scFv fragments, and generation of a large number of Fv sequences with improved binding affinity compared to non-mutagenized antibody. Notably, the authors stated "[t]he relative ease with which extremely high affinity has been attained in this study." (page 10705, first column, last full paragraph) Consequently, in view of the fact that functional variants with improved affinity could be made "with relative ease" at the time of the invention, one of skill in the art could produce variant antibodies and fragments having at least some detectable binding affinity, inhibit cell proliferation or induce apoptosis, without undue experimentation at the time of the invention.

To further corroborate that one of skill in the art could produce variant antibodies and fragments having at least some detectable binding affinity, inhibit cell proliferation or induce apoptosis without undue experimentation at the time of the invention, submitted herewith is a Declaration under 37 C.F.R. §1.132, executed by Dr. Peter Vollmers. As stated in the Declaration, Dr. Vollmers, based upon objective facts and conclusions based upon the objective facts, concludes that one of skill in the art, in view of the guidance in the specification and knowledge in the art at the time of the invention, could produce antibodies and functional fragments having binding activity without undue experimentation (Paragraph 20). The facts and Dr. Vollmers' conclusions based upon the facts are summarized in the Declaration, Paragraphs 20-24. Accordingly, the Declaration under 37C.F.R. §1.132, executed by Dr. Peter Vollmers corroborates that one of skill in the art could produce variant

antibodies and functional fragments having binding affinity, inhibit cell proliferation or induce apoptosis, without undue experimentation at the time of the invention.

Given the fact that one skilled in the art could make and identify variant antibodies and functional fragments without undue experimentation, as discussed above and at length in the record, there would be no reason to "predict which variation would not compromise antigen binding specificity." Again, the Patent Office inexplicably continues to insist that one skilled in the art must "predict which variation would not compromise antigen binding specificity" while ignoring the fact that one skilled in the art could make and identify variant antibodies and fragments without undue experimentation at the time of the invention. However, the Patent Office fails to explain why one of skill in the art must "predict which variation would not compromise antigen binding specificity," when prediction is not required to make and identify antibodies and fragments without undue experimentation. Furthermore, the Patent Office fails to provide any meaningful reason as to why one of skill in the art must use this particular methodology, namely, predicting variations that would not compromise antigen binding specificity, to the exclusion of other methodologies for making antibodies and functional fragments without undue experimentation.

There is no authority requiring that enablement be satisfied by a particular methodology identified by the Patent Office to the exclusion of other methodologies. Thus, the Patent Office's insistence that Applicants must demonstrate enablement under 35 U.S.C. §112, first paragraph by a particular methodology is not supported by the statute nor any case law and is therefore clearly improper. Consequently, the Patent Office's continued refusal to acknowledge that one skilled in the art could make and use variant antibodies and functional fragments without undue experimentation at the time of the invention, while insisting that the enablement requirement can only be satisfied by a particular method, clearly reveals that the Patent Office is applying an incorrect standard for enablement under 35 U.S.C. §112.

Turning to the grounds for rejection, due to certain claims allegedly being directed to single CDRs (page 10), as previously pointed out an antibody, by definition, includes three CDRs in each heavy and light chain variable region sequence. The claims, as amended, recite both light chain (V_L) and heavy chain (V_H) variable region sequences, in order to more clearly indicate that both are present. Thus, given that the claims require both a light chain (V_L) variable region and a heavy chain (V_H) variable region sequence, all 6 CDRs are present. Dependent claims 109 to 111, as amended, further specify the amino acid sequence of one or more of the CDRs in either the light chain (V_L) variable region and heavy chain

(V_H) variable region sequences. Accordingly, as all 6 CDRs are present this ground for rejection is therefore not applicable.

In sum, in view of the guidance in the specification and knowledge in the art at the time of the invention, and the corroborating Declaration under 37C.F.R. §1.132, executed by Dr. Peter Vollmers, the skilled artisan could readily produce and identify antibody variants and functional fragments of SEQ ID NO:1 and 3 without undue experimentation. Consequently, claims 73, 75, 80, 81, 100 to 112, and 115 to 121 are adequately enabled under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

WRITTEN DESCRIPTION

The rejection of claims 72 to 79, 82 to 88 and 98 to 116 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. According to the Patent Office, allegedly the claims contain subject matter which is not adequately described in the specification to reasonably convey to one skilled in the art that Applicants had possession of the invention.

The claims are adequately described under 35 U.S.C. §112, first paragraph. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, claims 72, 74, 76 to 79, 82 to 88, 98, 99, 113 and 114 have been cancelled without prejudice. The rejection will therefore be addressed as if applied to the amended claims.

Applicants first point out that with respect to the statement at page 13 of the Action that the claims are interpreted as drawn to any antibody that binds to the same antibody as the SAM-6 antibody, but "which epitope occurs on any number of antigens, expressed on the list of neoplastic cells," the claimed antibodies and functional fragments bind at least one deposited cell line, namely one of BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), or LOU-NH91 (DSMZ Accession No. ACC 393). Thus, the antibodies will bind to an epitope of an antigen expressed by at least one of these specifically recited cell lines, and to which epitope SAM-6 antibody also binds.

Furthermore, the Patent Office apparently believes that the possibility that an epitope may be present on more than one antigen, or that the epitope to which the claimed antibodies and functional fragments bind is not fully characterized, determines whether the claims are adequately described under 35 U.S.C. §112, first paragraph. However, antibody claims

where no antibody has ever been produced are routinely granted by the Patent Office even if the antibodies bind to epitopes that are possibly present on multiple antigens, or there is no knowledge concerning the epitope that the antibodies bind. Thus, if claims to antibodies that bind to epitopes possibly present on multiple antigens, or that bind to epitopes that have not been characterized are routinely granted by the Patent Office, surely knowing whether or not the epitope is present on multiple antigens or has been characterized is not required to satisfy written description under 35 U.S.C. §112, first paragraph. Thus, the mere possibility that an epitope to which an antibody binds may be present on more than antigen or is not fully characterized is insufficient to conclude that the claims do not satisfy the written description under 35 U.S.C. §112, first paragraph.

Applicants also respectfully point out that the statement at page 14 of the Action that the standard for written description under 35 U.S.C. §112, first paragraph, allegedly includes "actual reduction to practice" is not the proper standard. To the contrary, the law does not require an actual reduction to practice or disclosure of a specific number of examples within the scope of the claims to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976), *Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir. 1988). In particular, "(1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Consequently, actual reduction to practice is not required to satisfy written description under 35 U.S.C. §112, first paragraph.

A proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Possession is assessed from the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The description needed to satisfy the requirements of 35 U.S.C. §112 "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.....Since the law is applied to each invention in view of the state of the relevant

knowledge, its application will vary with differences in the state of the knowledge in the field and differences in the predictability of the science....the law must take cognizance of the scientific facts." *Capon v. Eshhar*, 418 F.3d , 1349, 1357 (Fed. Cir. 2005), emphasis added. Thus, an adequate written description is a factual inquiry measured by one of ordinary skill in the art that varies with the nature and scope of the invention, taking into consideration the scientific and technologic knowledge in existence in the relevant field.

Here, the claims comply with the written description requirement under 35 U.S.C. §112, first paragraph. First, the claimed antibodies and functional fragments bind to an epitope of an antigen that SAM-6 antibody comprising SEQ ID NO:1 and SEQ ID NO:3 binds, and the antigen is expressed by at least one of the specifically recited cell lines. Thus, the epitope of the antigen is defined in terms of 1) expression by at least one of the recited cell lines; and 2) binding to SAM-6 antibody comprising SEQ ID NO:1 and SEQ ID NO:3. Thus, one of skill in the art would know, without having to know more about the identity of the epitope or antigen, antibodies and functional fragments within the scope of the claims. For example, one skilled in the art would know that competition binding is a simple and routine technique known in the art at the time of the invention to verify that a given antibody or functional fragment binds to an antigen expressed by a cell. Thus, an antibody or functional fragment that competes for SAM-6 binding to antigen expressed by at least one of the specifically recited cell lines would be within the scope of the claims, whereas an antibody that did not compete for SAM-6 binding to antigen expressed by at least one of the specifically recited cell lines would not be within the scope of the claims. Consequently, one of skill in the art needs no more information about epitope or antigen identity in order to know antibodies and functional fragments within the scope of the claims.

Second, the claimed antibodies and functional fragments are described structurally and functionally. In particular, as recited in the claims and discussed above, the claimed antibodies and functional fragments bind to an epitope of an antigen to which SAM-6 antibody comprising SEQ ID NO:1 and SEQ ID NO:3 bind. Furthermore, members of antibody species that bind to a common epitope typically share sequence homology, such as in CDR3 of heavy chain variable region. Thus, antibodies that bind to the same epitope will inherently share sequence identity to SEQ ID NO:1 and/or SEQ ID NO:3. Further in this regard, antibodies and functional fragments of claims 100 to 106, 109 to 111, 117 to 120 specifically require sequence identity with SEQ ID NO:1 and/or SEQ ID NO:3. Thus, the claimed antibodies and functional fragments share a common functional (epitope binding)

and structural (sequence identity) relationship with SAM-6. Given the function and the sequence identity shared between the claimed antibodies and functional fragments and SEQ ID NO:1 and/or SEQ ID NO:3, the antibodies and functional fragments have well defined structural and functional features in common.

Third, the knowledge and skill in the art in terms of antibody structure correlating with function at the time of the invention was high. Namely, the role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding was well understood by the skilled artisan at the time of the invention. The specification also discloses the role of antibody heavy and light chain variable regions in antigen binding (page 29, line 16, to page 30, line 14). Consequently, the level of knowledge and skill in the art with respect to antibody structure (CDRs, FRs, D- and J-regions, etc.) correlating with function was high at the time of the invention. Furthermore, the specification discloses antibody variable light and heavy chain region sequences (e.g., SEQ ID NOs:1 and 3), the predicted sequences and positions of all CDRs (page 5, lines 11-21; and Sequence Listing), and therefore also the location of the FRs. Consequently, the skilled artisan would know the predicted locations and amino acid sequences of all CDRs and FRs of SEQ ID NOs:1 and 3 that contribute to antigen binding.

Fourth, because the knowledge and skill in the art in terms of antibody structure correlating with function was high and the predicted location and sequences of CDRs and FRs in SEQ ID NOs:1 and 3 that contribute to antigen binding would be known, the skilled artisan would also have known residues in SEQ ID NOs:1 and 3 amenable to substitution. For example, in view of the understanding of CDRs and FRs in antigen binding at the time of the invention, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, insertion or a deletion, for example, outside of a CDR or FR region of in SEQ ID NOs:1 and 3 would likely not destroy antigen binding activity. Furthermore, because the level of knowledge and skill in the art with respect to antibody structure correlating with function was high such that at the time of the invention one skilled in the art could have predicted with a high degree of confidence many substitutions of SEQ ID NOs:1 and 3 that would not destroy binding activity. Moreover, as previously pointed out, changes in antibody CDRs and FRs are more permissive than what the Patent Office acknowledges, as evidenced by previously submitted Exhibits B-E, each reporting that substitutions or deletions/insertions of amino acids within antibody CDRs (i.e., CDR1, CDR2 or CDR3) or FRs were well tolerated.

The facts of Applicants' claimed antibodies and functional fragments are analogous to the facts in *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005), in which the court held that a single embodiment of a protein (a reverse transcriptase (RT)) provided an adequate written description for claims directed to a genus of such proteins since the single disclosed protein embodiment had 1) sufficient correlation between structure and function; and 2) shared significant homology with others. In affirming that the patent claims satisfied the written description requirement, as articulated in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (1997) and *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), the court held that "the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features—DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient. In short, there is no error in the district court's ruling that the claims in the patents-in-suit satisfy the written description requirement of §112." Thus, the claims of the patents-in-issue in *Invitrogen*, which did not recite a particular amount of homology or identity to a reference sequence in the claims, satisfied the written description requirement even though there was only a single disclosed embodiment in the specification. In view of *Invitrogen*, a single embodiment provides an adequate written description of a genus of proteins where there is sufficient correlation between protein structure and function, and the members of the species share significant homology.

Here, there was substantial understanding of antibody structure correlating with function at the time of the invention, the specification discloses antibody light and heavy chain variable region sequences including predicted positions and sequences of all CDRs and therefore the location and sequences of all FRs, and as such all sequences that mediate antigen binding. The claimed antibodies and functional fragments also share common structural (sequence homology) and functional (bind to the epitope to which SAM-6 antibody binds) attributes. Consequently, the facts of the claims under consideration closely parallel the facts in *Invitrogen*.

The Patent Office cites *In re Alonso*, 545 F.3d 1015 (Fed. Cir. 2008) to support the rejection. However, *In re Alonso* is inapposite to this application because the facts and context underlying the claims under consideration are highly distinguishable from those that led to the *In re Alonso* decision.

First, the *Alonso* claims are directed to methods of treating neurofibrosarcomas, using antibodies idiotypic to the neurofibrosarcomas. Significantly, the antibodies in *Alonso* were not limited to binding to any particular epitope or antigen. Instead, the genus of antibodies encompassed by the *Alonso* claims could bind to any epitope and any antigen expressed, which epitopes and antigens had different and unknown specificities. Thus, the claimed treatment methods of *Alonso* encompassed antibodies not limited to binding to any particular epitope or antigen.

In contrast to the antibodies of *Alonso*, the claimed antibodies and functional fragments have identical specificity and bind to a single epitope, namely the epitope of the antigen expressed by at least one of the specified neoplastic cells recited in the claims to which the SAM-6 antibody comprising SEQ ID NO:1 and SEQ ID NO:3 specifically binds. Also in contrast to *Alonso*, the claimed antibodies and functional fragments bind to antigen expressed by at least one of 5 well defined deposited cell lines, namely BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), and LOU-NH91 (DSMZ Accession No. ACC 393) neoplastic cells.

Second, the antibodies in *Alonso* were not defined by or limited to any structure. In contrast to the *Alonso* antibodies, the claimed antibodies and functional fragments share a common structure due to 1) binding to the same epitope; and 2) claims 100 to 106, 109 to 111, 117 to 120 specifically recite various amounts of sequence identity to heavy and light chain variable regions (SEQ ID NOs:1 and 3) of SAM-6 antibody. Thus, the claimed antibodies and functional fragments share a common structure (amino acid residues) owing to binding to the same epitope, and as specifically recited in claims 100 to 106, 109 to 111, 117 to 120. The relevance of such claimed structure is illustrated by Xu and Davis (Immunity 13:37 (2000)), submitted herewith as Exhibit 1, whom reported that CDR3 of the heavy chain variable region was the primary determinant which confers antigen recognition and specificity, which did not require changes to CDR1 or CDR2 sequences. Consequently, the claimed antibodies and functional fragments will have a CDR3 heavy chain variable region with significant sequence identity to CDR3 of SEQ ID NO:3, whereas in the *Alonso* antibodies there was no structural relationship among the genus of antibodies.

Third, the patent application at issue in *Alonso* (USSN 08/469,749) claimed priority to an application filed in 1988. In contrast, the subject application claims priority to an application filed November 11, 2003, which is at least 15 years after the *Alonso* priority

application was filed. Obviously, the state of knowledge in the art concerning antibody structure correlating with function was greater in 2003 than in 1988. Indeed, the state of the art was so much more advanced in 2003 that a finding based upon the state of the art in 1988 is wholly insufficient to make a factual evaluation of an invention in 2003. As an example of the advanced state of the art, in 1992, a publication reported substitutions of framework residues of humanized antibodies with donor framework residues improved antibody affinity (Foote and Winter, J. Mol. Biol. 224:487 (1992), submitted herewith as Exhibit 2) indicating that FR residue substitutions are tolerated and can improve affinity. As another example of the advanced state of the art, two publications, in 1998 and 2000, reported that CDR3 of heavy chain variable region was the principal determinant of antigen recognition and specificity (Exhibit 1; see, also, Morea et al. J. Mol. Biol. 275:269 (1998), submitted herewith as Exhibit 3). In particular, the authors of Exhibit 1 reported that changes in heavy chain CDR3 amino acids accounted for the diversity of response against various protein antigens, and did not require changes to CDR1 or CDR2 sequences, indicating that one of skill in the art would know that heavy chain CDR1 and CDR2 are less important for antigen specificity compared to heavy chain CDR3. As yet another example of the advanced state of the art, a review publication by Padlan (Molecular Immunology 31:169 (1994), submitted herewith as Exhibit 4) report the role of FRs and CDRs in antibody function, that FRs have conserved substitutions (e.g., page 177), that CDR3 has a primary role in antigen specificity (page 196 second column), and that particular amino acid residues are more prevalent in CDRs/FRs (pages 197-198). Still another publication evidencing the advanced state of the art reported the construction of a fully human combinatorial antibody library based upon human consensus FRs and CDRs (Knappik et al., J. Mol. Biol. 296:57 (2000) submitted herewith as Exhibit 5). Consequently, one of skill in the art would know antibody sequence regions more or less amenable to substitution, the types of amino acid residues that are most prevalent and/or tolerated at given positions and could therefore deduce functional variants based upon this knowledge.

A further example of the advanced state of the art is a publication by Collet *et al.* (Proc. Nat'l. Acad. Sci. USA 89:10026 (1992), submitted herewith as Exhibit 6), whom reported that heavy chain variable region sequences could productively pair with a variety of different light chain variable region sequences and maintain antigen binding specificity (see, e.g., abstract, a heavy chain could productively pair with a light chain and still maintain HIV gp120 antigen binding activity from 43% -100%). Even unrelated light chain variable region

sequences (to tetanus toxoid) productively paired with a heavy chain variable region sequence (to HIV gp120) to produce an antibody that maintained binding to HIV gp120 with a high degree of frequency (page 10029-10030). Thus, one of skill in the art would have known that the heavy chain variable region sequence can productively pair with a number of light chain variable region sequences and retain antigen specificity, indicating that variations to the light chain variable region sequence are tolerated.

Thus, the knowledge in the art concerning antibody structure correlating with function was significantly greater in 2003 than in 1988. Consequently, in view of the high level of knowledge and skill in the art, one of skill in the art would have been able to reasonably predict with a high degree of confidence variants of SEQ ID NO:1 and 3 that would retain binding.

Furthermore, in view of the fact that the claimed antibodies and functional fragments have identical specificity, bind to a single epitope and share a common structure, unlike the *Alonso* antibodies, and that the state of the art at the time of that the application was filed was more advanced as compared to the state of the art of the application at issue in *Alonso*, the claims under consideration are highly distinguishable from the *Alonso* decision.

Lastly, but significantly, the Appellants in the *Alonso* decision failed to timely present the argument that the neurofibrosarcoma antibodies were adequately described in view of the well-known correlation between structure and function of antibodies. Thus, the *Alonso* court did not consider the merits of this argument since it was not raised during proceedings before the Board. Consequently, given the fact that arguments pointing out the well-known correlation between structure and function of antibodies were not considered by the *Alonso* court, the *Alonso* decision does not stand for the proposition that antibodies are not adequately described in spite of well-known correlation between structure and function of antibodies, particularly given the advances in the state of the art in the 15 years after the *Alonso* priority application was filed.

In sum, a proper analysis of the description requirement under 35 U.S.C. §112, first paragraph, requires a factual inquiry and consideration of the state of the knowledge in the relevant field. Here, the facts of the claimed antibodies and functional fragments are readily distinguishable from *Alonso*. Namely, unlike *Alonso*, the claimed antibodies and functional fragments 1) have identical specificity and bind to a single epitope that expressed by at least one of five well-defined deposited cell lines; 2) share a common sequence structure due to binding to a single epitope and as specifically recited in claims 100 to 106, 109 to 111, 117 to

120; and 3) unlike *Alonso*, the knowledge in the art concerning antibody structure correlating with function was far more advanced in 2003 than in 1988, the priority date of the *Alonso* application. Furthermore, in reaching its decision the *Alonso* court failed to consider the well-known correlation between structure and function of antibodies.

Additionally, the accompanying Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers verifies that the claims are adequately described under 35 U.S.C. §112, first paragraph. Dr. Vollmers provides objective facts, and conclusions based upon the objective facts, in the accompanying Declaration.

In terms of antibodies and functional fragments that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:1 and a heavy chain variable region sequence at least 75% identical to SEQ ID NO:3, Dr. Vollmers declares and states at paragraphs 6 to 15 of the Declaration that:

One skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and functional fragments that specifically bind to at least one of the recited cell lines as recited, and (i) that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:1, and comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:3; (ii) that comprise a light chain variable region sequence at least 80% identical to SEQ ID NO:1, and comprise a heavy chain variable region sequence at least 80% identical to SEQ ID NO:3; (iii) that comprise a light chain variable region sequence at least 85% identical to SEQ ID NO:1, and comprise a heavy chain variable region sequence at least 85% identical to SEQ ID NO:3; (iv) that comprise a light chain variable region sequence at least 90% identical to SEQ ID NO:1, and comprise a heavy chain variable region sequence at least 90% identical to SEQ ID NO:3; or (v) that comprise a light chain variable region sequence at least 95% identical to SEQ ID NO:1, and comprise a heavy chain variable region sequence at least 95% identical to SEQ ID NO:3.

Dr. Vollmers' conclusions are based upon the following objective facts: The specification discloses the light chain variable region amino acid sequence, SEQ ID NO:1, and heavy chain variable region amino acid sequence, SEQ ID NO:3. The specification discloses that light and heavy chain variable region sequences SEQ ID NOs:1 and 3 are derived from a human antibody (Example 2). The specification also discloses the predicted sequence of all three CDRs in the variable region sequences (see, for example, page 5, lines 8-21, and page 2, lines 19-30, and the sequence listing). Dr. Vollmers therefore concludes

that the skilled artisan would know the sequence and the predicted locations of the three CDRs in light and heavy chain variable regions.

Dr. Vollmers' furthermore declares that as the predicted locations of the three CDRs in SEQ ID NOs:1 and 3 would be known to the skilled artisan and that SEQ ID NOs:1 and 3 are derived from a human antibody, the skilled artisan would also have known the location of the framework regions (FRs) in SEQ ID NOs:1 and 3, as well as the D- and J-regions in SEQ ID NOs:1 and 3. Dr. Vollmers therefore declares that the skilled artisan would know the sequence and location of amino acid residues of SEQ ID NOs:1 and 3 that contribute to antigen binding.

Dr. Vollmers declares that the level of knowledge and skill in the art concerning antibody structure and function at the time of the invention was high. As evidence of the high level of knowledge and skill in the art, the specification discloses the function of antibody heavy and light chain variable (e.g., CDR and FR) and constant regions (page 29, line 16, to page 30, line 14). The role of variable region sequences, including CDRs in antigen binding known in the art at the time of the invention (see, for example, Immunology, Goldsby, R.A., 5th ed. W.H. Freeman, 2002).

Dr. Vollmers also declares that because the amino acids of light and heavy chain variable region sequences SEQ ID NOs:1 and 3 that contribute to antigen binding would be known to one of skill in the art in view of the specification and the high level of knowledge and skill in the art concerning antibody structure and function, the skilled artisan would have known a number of antibodies and functional fragments with amino acid residues of SEQ ID NOs:1 and 3 that could be substituted (i.e., would likely not destroy binding activity). Consequently, the skilled artisan would envision light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:1, and heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:3 that would have at least partial activity.

Dr. Vollmers illustrates the foregoing by way of the example of an amino acid substitution. In brief, an amino acid substitution such as a non-conservative or conservative substitution outside a CDR or FR region of SEQ ID NOs:1 or 3 would likely not destroy binding activity of an antibody, and conservative substitutions within a CDR or FR region of SEQ ID NOs:1 or 3 would also likely not destroy binding activity of an antibody or antigen binding fragment. Dr. Vollmers thus declares that the skilled artisan would know of a number of antibodies and antigen binding fragments comprising SEQ ID NO:1 or 3 with non-

conservative or conservative substitutions located outside of a CDR or FR of SEQ ID NO:1 or 3, or conservative substitutions within a CDR or FR of SEQ ID NO:1 or 3, that likely retain at least partial binding activity.

Dr. Vollmers points out that typically about half of the amino acids in a given heavy or light chain variable region sequence is not within one of the three CDRs. Dr. Vollmers concludes that because there are a large number of amino acids outside of the CDRs, the skilled artisan would envision a number of residues outside of CDRs that could be substituted and likely retain at least partial binding activity. Thus, Dr. Vollmers declares that the skilled artisan would readily envision antibodies and antigen binding fragments with light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:1, and heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:3, that would retain at least partial binding activity without actually having to verify that the variant has at least partial binding activity.

Dr. Vollmers further declares that not only would the skilled artisan envision antibodies and antigen binding fragments with light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:1, and heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:3, that retain at least partial binding activity, but would also know nonfunctional variants. For example, the skilled artisan knows that heavy chain variable region CDR3 appears to confer fine binding specificity, and therefore that a large number of non-conservative substitutions, insertions or deletions of heavy chain variable region CDR3 would likely result in loss of antigen specificity. Dr. Vollmers therefore concludes that the skilled artisan would also know of SEQ ID NOs:1 and 3 with sufficient substitutions, insertions or deletions such that the antibody or functional fragment would be unlikely to have binding activity.

Dr. Vollmers moreover declares that the ability of the skilled artisan to envision sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:1 and sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:3 that would retain at least partial binding activity is further evidenced by the fact that humanizing antibodies was known at the time of the invention (see, for example, U.S. Patent No. 6,180,370). In particular, Dr. Vollmers points out that grafting non-human CDRs to human framework sequences to form an antigen binding antibody was well established at the time of the invention. Dr. Vollmers concludes that because all CDRs of a given variable region

sequence could be transferred from one mammalian species to another without destroying binding activity of the resultant antibody, the skilled artisan would readily envision antibodies and antigen binding fragments could comprise CDRs of one species and fragments of another without destruction of antigen binding activity that comprise light chain variable region sequences with 75% or more identity to SEQ ID NO:1, and heavy chain variable region sequences with 75% or more identity to SEQ ID NO:3. Moreover, Dr. Vollmers concludes that given that humanized antibodies retain binding and that variable region sequences can include non-identical amino acids in many positions outside of the CDRs without destroying binding activity, variants can be substantially non-identical to SEQ ID NOs:1 and 3 outside of the CDRs while retaining binding activity. Dr. Vollmers thus concludes that the skilled artisan would readily envision a number of antibodies and antigen binding fragments that vary in positions outside of the CDRs of SEQ ID NOs:1 and 3 that retain at least partial binding activity.

To illustrate that substitutions within CDRs are tolerated, Dr Vollmers refers to previously submitted Exhibit B (Kipriyanov *et al.*, Protein Engineering 10:445 (1997), whom report that a substitution of a cysteine residue by a serine within CDR3 of an antibody heavy chain variable region did not have an adverse effect on binding affinity. Thus, Exhibit B corroborates that the skilled artisan would know that a substitution of a light or heavy chain variable region CDR residue are tolerated and would not necessarily destroy binding activity.

To illustrate that substitutions within FRs can generally be tolerated, Dr. Vollmers refers to previously submitted Exhibit C (Holmes *et al.*, J. Immunol. 167:296 (2001)), whom report that several heavy chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity. Thus, Dr. Vollmers' concludes that antibodies and antigen binding fragments with a substitution of a light or heavy chain variable region FR residue are tolerated and would not destroy binding activity.

Concerning antibodies and functional fragments that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:1 and a heavy chain variable region sequence at least 75% identical to SEQ ID NO:3, wherein the light or heavy chain variable region sequence has an insertion or deletion of one amino acid residue, Dr. Vollmers declares and states at paragraphs 16 to 19 of the Declaration that:

One skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and antigen binding fragments that specifically

bind to a polypeptide expressed by at least one of the recited cell lines and that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:1 and a heavy chain variable region sequence at least 75% identical to SEQ ID NO:3, wherein the light or heavy chain variable region sequence has an insertion or deletion of an amino acid residue (paragraph 16).

Dr. Vollmers' conclusions are based upon the following objective facts: Again, the sequence of amino acid residues of light and heavy chain variable region sequences SEQ ID NOs:1 and 3 and corresponding CDRs, FRs, etc., that contribute to antigen binding would be known, and the level of knowledge and skill in the art concerning antibody structure and function was high. Consequently, the skilled artisan would have known antibodies and fragments with substitutions of SEQ ID NOs:1 and 3 that would not destroy binding activity, and therefore would envision variable region sequences with 75% or more identity to SEQ ID NO:1 and 3 (e.g., 80%, 85%, 90%, 95%, etc.) with at least partial activity. In addition, an amino acid insertion or deletion of SEQ ID NOs:1 or 3 would also likely not destroy binding activity of an antibody (paragraph 18).

To corroborate the foregoing conclusions concerning insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, Dr. Vollmers points out that such alterations occur during antibody affinity maturation, and refers to previously submitted Exhibit D (Wilson *et al.*, J. Exp. Med. 187:59 (1998)), whom report a number of insertions and deletions of variable heavy chains that occur naturally during affinity maturation. Dr. Vollmers therefore concludes that the skilled artisan would know with a high degree of confidence that an antibody or antigen binding fragment comprising SEQ ID NO:1 or 3 with an amino acid insertion or deletion within or outside of a CDR, would very likely retain at least partial binding activity.

To further corroborate Dr. Vollmers' conclusions that antibodies and antigen binding fragments with a light or heavy and chain variable region sequence insertion or deletion can be tolerated, even within a CDRs, he refers to previously submitted Exhibit E (Lantto and Ohlin, J. Biol. Chem. 277:45108 (2002), whom report that single amino acid insertions or deletions of CDRs 1 and 2 of heavy chain variable region of an antibody were well tolerated. Thus, Exhibits D and E corroborate that antibodies and antigen binding fragments that comprise a light or heavy chain variable region sequence insertion or deletion, even within a CDR, can be tolerated (paragraph 19).

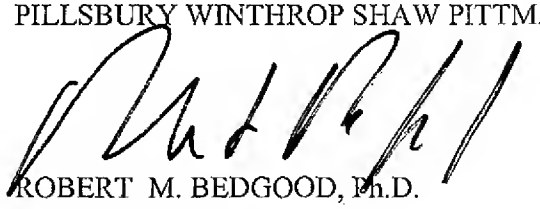
In sum, given the totality of: Guidance in the specification and the high level of knowledge and skill in the art with respect to antibody structure correlating with function at the time of the invention, knowledge of the light and heavy chain variable region sequences (SEQ ID NOs:1 and 3) and the CDRs and FRs that confer binding, and as also corroborated by the Declaration under 37 C.F.R. §1.132 executed by Dr. Vollmers submitted herewith and previously submitted Exhibits B-E, the skilled artisan would know of general regions and particular residues that would be amenable to variation and would therefore be apprised of a number of sequence variants of SEQ ID NOs:1 and 3 having binding activity, the claims meet the written description standard articulated by the court in *Invitrogen*. Further in view of the substantially greater understanding of antibody sequence structure and correlation with function in 2003 compared to 1988, and that the claimed antibodies and fragments will bind to the same epitope as SAM-6 antibody comprising SEQ ID NOs:1 and 3, and will also necessarily have sequence homology with SEQ ID NOs:1 or 3, the facts of the claims under consideration are clearly distinguishable from the facts in *Alonso*. Consequently, claims 73, 75, 80, 81, 100 to 112, and 115 to 121 are adequately described under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

CONCLUSION

Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP



ROBERT M. BEDGOOD, Ph.D.
Reg. No. 43488
Tel. No. 858.509.4065
Fax No. 858 509.4010

Date: November 5, 2009
12255 El Camino Real, Suite 300
San Diego, CA 92130-4088
(619) 234-5000

CERTIFICATION UNDER 37 C.F.R. §§ 1.8 and/or 1.10*

(When using Express Mail, the Express Mail label number is *mandatory; Express Mail certification is optional.)*

I hereby certify that, on the date shown below, this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: _____

Signature

Patricia Munoz
(type or print name of person certifying)

** Only the date of filing (§ 1.6) will be the date used in a patent term adjustment calculation, although the date on any certificate of mailing or transmission under § 1.8 continues to be taken into account in determining timeliness. See § 1.703(f). Consider "Express Mail Post Office to Addressee" (§ 1.10) or facsimile transmission (§ 1.6(d)) for the reply to be accorded the earliest possible filing date for patent term adjustment calculations.*